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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/147,346	03/01/99	YARKONI S	1268-073

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LOWE HAUPTMAN GOPSTEIN
GILMAN & BERNER
1700 DIAGONAL ROAD
SUITE 310
ALEXANDRIA VA 22314

EXAMINER	
HELMS,L	
ART UNIT	**PAPER NUMBER**
1642	11

DATE MAILED: 04/26/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/147,346	Yarkoni et al
Examiner	**Group Art Unit**
Larry R. Helms Ph.D.	1642

☒ Responsive to communication(s) filed on *1 Mar 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-7 and 9-22* is/are pending in the applicat

Of the above, claim(s) *11-20 and 22* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-7, 9, 10, and 21* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *10*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 1-7, 9-10, and 21 in Paper No. 8 is acknowledged. The traversal is on the ground(s) that the "novel, patentable materials are useful to treat several different diseases...these diseases are all different, but all are treatable with the compositions". In addition, the traversal is on the grounds that "the claimed product is made by the claimed method and the claimed method produces the claimed product." This is not found persuasive. As stated in the response on page 3 restriction is appropriate if the product can be made by a different method. As evidenced by Nett (WO 90/09799, published 07/09/90, IDS, paper # 10) the gonadotropin releasing hormone chimeric toxin can by produced by a method of chemical conjugation in addition to the method described in claim 1 by genetic engineering techniques (see abstract). Applicants are correct in that the product can be used for treating several diseases, however, as stated in the response "These diseases are all different" and the treatment of each of these diseases would require different issues and the literature search, particularly relevant in this art, and is not co-extensive and is much more important in evaluating the burden of search. As to the question of burden of search, classification of subject matter is merely one indication of the burdensome nature of the search involved. Clearly different searches and issues are involved in the examination of each group. With regard to applicants argument about claim 8, which was inadvertently included in Group I, it is noted that claim 8 was canceled

in Preliminary Amendment A filed 12/4/98 and will not be examined. For these reasons the restriction requirement is deemed to be proper and is made **FINAL**.

2. It is pointed out that applicants have presented added claim 22 in improper format. The claim is improperly joined as the various groups appear to encompass distinct targets for treating a disease to such an extent that they are considered separately patentable. A reference against one would not be a reference against the other. Therefore, a restriction will be set forth for each of the various groups, irrespectively of the improper format of the claims, because these are not proper species.

3. Newly submitted claim 22 is directed to an invention that is encompassed by Groups I-VI in the original restriction requirement. As applicants have pointed out in the response to the restriction requirement "these diseases are all different" (see page 2-3 of Paper #8). As such, art on one disease would not be art on the other diseases. Therefore, claim 22 will be examined to the extent that the claim reads on a method for treating cancer as this part of the claim is encompassed in the elected Group I claims.

4. Claims 11-20 and claim 22 in part are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Applicant timely traversed the restriction (election) requirement in Paper No. 8.

5. This application contains claims drawn to an invention nonelected with traverse in Paper No. 8. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

6. Claims 1-7, 9-10, 21, and claim 22 in part are under examination.

Specification

7. The disclosure is objected to because of the following informalities:

a. The first line of the specification should indicate that the present application is a 371 national phase filing of PCT/IL97/00180, filed 06/04/97.

b. Page 6 has "*****" at line 5 from the bottom of the page.

Appropriate correction is required.

Drawings

8. The drawings are considered to be informal because they fail to comply with 37 CFR 1.84(a)(1) which requires black and white drawings using India ink or its equivalent.

a. Photographs and color drawings are acceptable only for examination purposes unless a petition filed under 37 CFR 1.84(a)(2) or (b)(1) is granted permitting their use as formal drawings. In the event applicant wishes to use the drawings currently on file as formal drawings, a petition must be filed for acceptance of the photographs or color drawings as formal drawings.

Any such petition must be accompanied by the appropriate fee as set forth in 37 CFR 1.17(I), three sets of drawings or photographs, as appropriate, and, if filed under the provisions of 37 CFR 1.84(a)(2), an amendment to the first paragraph of the brief description of the drawings section of the specification which states:

> The file of this patent contains at least one drawing executed in color. Copies of this patent with color drawing(s) will be provided by the Patent and Trademark Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings have been satisfied.

b. Figure 3A-3F need to have separate axis labels for each view.

Appropriate correction is required.

Claim Objections

9. The claims are objected to because of the following informalities:

a. Claim 2 is objected to for it is not clear if a comma has been placed after the term "uterine".

b. Claims 7 and 9 are objected to for reciting "claims 1".

c. Claim 22 is objected as it directed to non-elected inventions.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

10. Claims 1-7, 9-10, 21, and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-7, 9-10, 21, and 22 are indefinite for reciting in claim 1 "targeted fused chimeric toxins" as the exact meaning of the phrase is not clear. Is "fused" meant to be chemically conjugated, covalently coupled, or two DNA fragments ligated together, or some other meaning? As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims.

b. Claims 1-7, 9-10, 21, and 22 are indefinite for reciting in claim 1 "produced by genetic engineering techniques" for the exact meaning of the phrase is not clear. Does the phrase mean the entire chimeric toxin is produced by genetic engineering techniques or is the toxin itself produced by genetic engineering and the targeting moieties are produced by some other method? As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims.

c. Claims 1-7, 9-10, 21, and 22 are indefinite for reciting in the claims "toxins" and "moieties" for it is not clear if applicants mean these terms in the plural or singular? Does the plural term "moieties" consist of singular "hormone" or a single "toxin"? In addition, claim 21 recites "chimeric toxin as defined in claim 1" and claim 1 recites "chimeric toxins". As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims.

d. Claims 1-7, 9-10, 21, and 22 are indefinite for it is not clear if the cell killing moiety recognizes the cell or does the cell targeting moiety recognize the cell? As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims.

e. Claim 2 is indefinite as being structured as an improper Markush claim. Proper Markush claims are in the format of "X is selected from a group consisting of A, B, C, and D," or "the X is A, B, C or D" (See MPEP 2173.05(h)).

f. Claim 3 is indefinite for reciting "a mutated sequence" for the exact meaning of the phrase is not clear. It is not clear how or which positions in the sequence are to be mutated. As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims.

g. Claims 3 and 4 are indefinite for it is not clear if the sequence or the exotoxin encodes the protein. As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims.

h. Claims 5, 6, 9 recites the limitation ""targeted fused chimeric toxin GnRH-PE66 as defined in claim 1" in claim 5 and "a method for the production of cancer cell targeted chimeric

toxin GnRH-PE40 as defined in claim 1" in claim 6 and "or their pharmaceutical compositions as defined in claims 1" . There is insufficient antecedent basis for these limitation in claim 1.

I. Claims 5, 6, 9, 10, and 22 are indefinite for reciting incomplete method claims which do not clearly set forth method steps and does not include a resolution step which reads back on the preamble of the claimed method. Claim 5 recites an incomplete method for "fusing an oligonucleotide" comprising the hormone and a toxin which would not result in producing the toxin as claimed in the preamble. Claim 6 recites an incomplete method for "ligating an oligonucleotide" comprising the hormone and a toxin which would not result in producing the chimeric toxin as claimed in the preamble. Claims 9 and 10 recite a method for cancer therapy but it is not clear what the result of the method is. Claim 22 recites a method of treating cancer but it is not clear how it is treated or what the result of the method is. The claims should conclude with a resolution step that reads back on the preamble of the claimed method. As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims.

j. Claim 5 is indefinite for reciting "mutated form of PE"for it is not clear how or what residues are to be mutated in PE or what the term "mutated" encompasses. As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims.

k. Claim 9 recites the limitation "patient's body" in the claim. There is insufficient antecedent basis for this limitation in the claim.

l. Claims 3-6 are indefinite for reciting "analog" for the exact meaning of the term is not clear. The term "analog" is not one which has a universally accepted meaning in the art. The primary deficiency in the use of this phrase is the absence of a ascertainable meaning for said phrase. Since it is unclear how the gonadotropin releasing hormone is to be altered to yield the class of analog referred to in the claims, there is no way for a person of skill in the art to ascribe a discrete and identifiable class of compounds to said phrase. Further, it is not clear whether the "analog" is formed by attachment of a detectable marker, therapeutic molecule, some other molecule or altering the amino acid sequence, for examples. As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims.

m. Claim 3 and 4 are indefinite for reciting "sequence" as it not clear how "fusing" an oligonucleotide coding for an amino acid to a "sequence" is performed. The term "sequence" refers to information describing the nucleic acid or amino acid sequence. Information is not a chemical structure, therefore, it is not clear how "sequence" can be linked to nucleic acid molecules. Replacing this term with polynucleotide, DNA, RNA or polypeptide, as appropriate, would be sufficient to obviate this rejection.

n. Claims 3-6 are indefinite for reciting "GnRH-PE66" and "GnRH-PE40" because other laboratories/inventors may use the same laboratory designation to refer to different proteins. Amendment of the claim to insert the corresponding SEQ ID NOs of the proteins would overcome this rejection.

o. Claims 3-6 are indefinite because they contain the abbreviation "GnRH" and "PE". Full terminology should be in first instance of the claims followed by the abbreviation in parentheses. Dependent claims may then use the abbreviation. Abbreviations render the claim indefinite because the same abbreviation may represent more than one element or concept.

p. Claims 5-6 are indefinite for reciting "fusing" or "ligating" an oligonucleotide encoding the hormone analog upstream to PE for the exact meaning is not clear. Are the claims intended to mean "fusing" or "ligating" DNA encoding the hormone to DNA encoding the PE or is the DNA "fused" or "ligated" to the protein?

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-7, 9-10, 21, and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a protein toxin comprising (1) the gonadotrophin releasing hormone (wherein the tryptophane at position 6 is replaced by a glycine residue) wherein the specific GnRH binding sites are on colon, breast, prostate, ovarian endometrium, renal , and liver carcinomas and (2) domains II and III of PE, the plasmid encoding such, the method of producing such, compositions comprising such, and a method for administering such compositions to a patient or treating cancer in vitro using such, does not reasonably provide enablement for a protein toxin comprising (1) any gonadotrophin releasing hormone analog and

(2) the full length PE or any mutated form of PE or any toxin other than PE, or pharmaceutical compositions comprising such or an in vivo method for cancer therapy or treatment in mammals including humans to target cells that do not have the GnRH receptor or to target any cancer cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use and practice the invention commensurate in scope with these claims.

a. Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

b. The claims are broadly drawn to protein toxins comprising (1) gonadotrophin releasing hormone analog and (2) any toxin, including the full length PE toxin, or any mutation in the PE toxin, pharmaceutical compositions comprising such, and a method for any in vivo cancer therapy or treatment of any cancer or cancer cells in mammals which includes humans by administering such fusion protein toxins.

c. The specification teaches that pseudomonas Exotoxin A (PE) based toxin proteins were constructed by (1) ligating an oligonucleotide encoding GnRH (tryptophane at position 6 is

replaced by glycine) to the DNA encoding a mutated form of PE generating GnRH-PE66 or (2) ligating an oligonucleotide encoding GnRH (Y to G at positions 6) to DNA encoding domains II and III of PE generating GnRH-PE40 (see page 5, lines 2-11). The specification teaches the effect of such proteins on various cell lines which have the GnRH receptor including cancer cell lines in vitro and primary cultures originating from cancer patients (see pages 11-16). The specification is silent as to the mutation in Domain I of PE for the generation of GnRH-PE66. The specification fails to teach any specific mutation in the PE as claimed. The specification does not enable any other toxin other than PE or pharmaceutical compositions comprising the toxin fusion proteins comprising GnRH or a method for any in vivo cancer therapy or treatment targeting any cancer cells that do not have the GnRH receptor in any mammal including humans by administering the protein fusion toxins comprising GnRH and PE.

d. Claims 1-6 are broadly drawn to targeted toxins comprising any toxin, or a full length PE toxins and mutant PE toxins and GnRH or GnRH "analog". The claims broadly encompass any toxin coupled to GnRH and as such the instant application fails to enable these compounds comprising any toxins. Lombardo et al (WO 93/15751, published 19/09/93, IDS # 10) states that "hybrid molecules formed between Pseudomonas exotoxin A and specific "targeting agents" can bind to many normal cells in the addition to the cells recognized by the "targeting agent". (see page 8, lines 24-26). Lombaro et al further states a truncated form of PE has been produced that no longer is capable of binding to mammalian cells which is called Pseudomonas exotoxin-40 (see page 9, lines 2-8). Thus, one skilled in the art would reasonable conclude that a fusion

protein comprising the full length form of PE would result in targeting problems or non specific binding to non targeted cells.

e. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of PE proteins broadly encompassed by the claims of a mutant form of PE and the broadly claimed GnRH "analog"and the claims broadly encompass a significant number of species. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar biological activity requires a (1) knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e., expectantly intolerant to modification), and (2) detailed knowledge of the ways in which the protein's structure relates to its function.

f. While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar biological activity are limited in any protein. The result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modification shown for a given protein to diminish with each further and additional modification, e.g., multiple substitutions. The sequence of some proteins

is highly conserved and one skilled in the art would not expect tolerance to any amino acids modifications in such proteins.

g. The specification does not support the broad scope of the claims which encompass all modifications because the specification does not disclose the following:

i. The general tolerance to modification and extent of such tolerance;

ii. The specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical;

iii. What fragments, if any, can be made which retain the biological activity of the intact protein; and

iv. The specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

h. Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed protein in manner reasonable correlated with the scope of the claims broadly including any number of additions, deletions, or substitutions and fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the protein's structure and still maintain biological activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F,2d

1200, 18 USPQ 1016 (Fed. Cir. 1991) at 18 USPQ 1026 1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986).f

I. Amending claims 1-6 to recite the specific forms of the GnRH "analog" which retain binding to the receptor and defining the specific toxin or PE by defining the domains or mutated residues which retain the toxic activity of the toxin would be sufficient to obviate this portion of this rejection.

j. Claims 7, 9-10, and 22 are broadly drawn to a method for any in vivo cancer therapy or treatment in any mammal by administering a toxin fusion protein comprising any toxin and GnRH. The claims broadly are drawn to a method of treating any cancer and any tumor.

Applicant has demonstrated that the targeted fused chimeric toxins of the instant application can be used to target colon, breast, prostate, ovarian endometrium, renal , and liver carcinomas. However, the claims broadly read upon the treatment of all types of cancer. As disclosed in Johnson et al (Cancer Treatment Review Vol 2 1-31 1975), Table 2, only certain types of agents can treat certain types of cancer and that the same compound is not effective in the treatment of all types of cancers. One skilled in the art would reasonably conclude from Johnson et al that not all cancers are going to be targeted or that not all cancers are going to be effected by a treatment with the claimed fusion proteins.

k. In addition, Jain discloses the art known barriers to the delivery of drugs into solid tumors (Scientific American July 1994). Impediments to drug delivery include (1) Nonuniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic

agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61); (3) High liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (page 61, Col. 1 paragraph 1); (4) Convection is a necessary mechanism by which larger therapeutics molecules such as antibodies, reach target cells which are not directly fed by the vasculature. Convection is not observed in large tumors (defined as more than ½ centimeter in diameter, page 62 col. 1) and convection is necessary for adequate drug delivery of molecules having a molecular weight of more than 5000 (page 61, col. 1 through page 63, col. 3) and (4) Molecules as large as antibodies (i.e., MW=150,000) would require several months to reach a uniform concentration in a tumor that measures 1 centimeter in radius (page 63, col. 2).

l. Chatterjee et al state the art recognized experience that for any novel therapy, the transition for the laboratory to the clinic (animal experiments to the bedside) is a quantum leap (Cancer Immunol. Imunother., 1994, see Introduction). Results obtained under controlled conditions and in inbred animals often differ from the clinical response obtained in patients. This applies to strategies drawn to cancer therapy. For example, Dermer states that the widely disparate character of human tumor cells contributes greatly to chemotherapy's continued ineffectiveness against cancer (Biotechnology 12: 320, 1994). Tumor burden and antigenic drift continue to present serious burdens for successful cancer therapy in vivo. Tumors are classified

as immunogenic or non-immunogenic, solid or hematological in nature. Effective cancer strategies should be designed to deal effectively with the nature of each of these classifications.

m. The specification does not disclose whether the method is effective in animals with pre-existing tumors, and this is a significant omission in view of the well-known immunosuppressive effects of certain tumors. The criticality of a working example encompassing all of the method steps, especially the treatment of pre-existing neoplasia, is underscored by Gura et al (Science Vol 278 11/97 1041-1042) in a discussion of potential shortcomings of extrapolating from in vitro studies and animal studies to similar procedures in cancer patients. Gura et al teaches that "xenograft tumors don't behave like naturally occurring tumors in humans" (page 1041, second col, second full paragraph) and that there were "gross difference in sensitivity in real tumors in mice and in the clonogenic assay" (page 1042, second col, second full paragraph). Further, Gura teaches that clonogenic assays "cannot tell researchers how anticancer drugs will act in the body" (page 1042, first-second col, bridging paragraph). One skilled in the art would reasonably conclude that evidence obtained in mouse xenograft models would not correlate with results expected in humans patients.

n. At the time the invention was made, pharmaceutical compositions comprising the claimed toxin comprising GnRH polypeptides were not routinely used for the treatment of cancer. The specification lacks guidance by way of general methods or working examples which teach the polypeptide which would be used for this purpose. Lack of working examples is given added weight in cases involving an unpredictable and undeveloped art, such as cancer therapy. It

is unpredictable whether the claimed pharmaceutical composition. Further, it is not routine in the art of cancer therapy to use compositions analogous to the claimed compositions for this purpose. Accordingly, there is no objective basis upon which the skilled artisan would reasonably be able to determine or predict an amount of the claimed composition effective for its intended use. Therefore, undue experimentation would be required to make and use the invention.

o. Therefore, due the unpredictability in the art as evidenced by Jian, Chatterjee et al, Dermer, and Gura et al and in view of the insufficient guidance and/or working examples concerning the use of the broadly claimed fusion protein toxin antibodies as agents for in vivo cancer therapy or treatment in mammals including humans, one skilled in the art would not know how to practice the broadly claimed invention without undue experimentation.

p. Claim 7 is drawn to a pharmaceutical composition of protein toxin comprising GnRH of claim 1. Enablement of a "pharmaceutical composition" is considered to rest on a teaching of in vivo administration for purposes consistent with the intended use disclosed in the specification. The disclosed intended use for the claimed pharmaceutical composition is for the treatment of cancer. The specification apparently does not discloses the claimed composition, and general methods for formulating compositions in pharmaceutically acceptable carriers, there is insufficient guidance which would enable one skilled in the art to use the claimed compositions for their intended purpose, viz., for the method of cancer therapy.

q. Amending claim 7 by removing the term "pharmaceutical" before the term composition should be sufficient to obviate this portion of this rejection for claim 7.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1-2, and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Nett et al (WO 90/09799, published 9/7/90, IDS paper # 10).

a. The claims recite a targeted fused gonadotropin releasing hormone comprising a cell targeting moiety consisting of gonadotropin releasing hormone and a cell killing toxin wherein the cells bearing the gonadotropin releasing hormone binding sites are malignant adenocarcinoma cells and compositions comprising such proteins. Applicant is reminded that the intended use of a product claim carries no patentable weight [MPEP 2111.02] for this rejection.

The method in which the targeted fused chimeric toxins were produced is immaterial to their patentability. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product I in the product-by-process claim I is the same or obvious from a product of the prior art, the claim is unpatentable even

though the prior product was made by a different process." *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

b. Nett et al teach conjugation of gonadotropin releasing hormone (GnRH) to toxins and the GnRH is used to target cells bearing GnRH binding sites and the toxin is employed to permanently destroy cells (see page 13, lines 24-35). Nett et al also teach compositions comprising such proteins (see page 36, lines 8-12).

15. Claims 1, 2, and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Lombardo et al (WO 93/15751, published 8/19/93, IDS paper # 10)

a. The claims have been described supra. Applicant is reminded that the intended use of a product claim carries no patentable weight [MPEP 2111.02] for this rejection.

The method in which the targeted fused chimeric toxins were produced is immaterial to their patentability. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product I in the product-by-process claim I is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

b. Lombardo et al teach GnRH coupled to cell killing molecules of PE and the GnRH is the "targeting agent" which targets cells bearing the GnRH receptor (see page 7, lines 20-26 and

page 9, lines 10-15). Lombardo et al also teach compositions comprising such (see page 22, lines 3-9). Applicant is reminded that the intended use of a product claim carries no patentable weight [MPEP 2111.02] for this rejection.

16. Claims 1, 2, and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Rusiecki et al (IDS paper # 10).

a. The claims have been described supra. Applicant is reminded that the intended use of a product claim carries no patentable weight [MPEP 2111.02] for this rejection.

The method in which the targeted fused chimeric toxins were produced is immaterial to their patentability. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product I in the product-by-process claim I is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

b. Rusiecki et al teach GnRH coupled to PE in which the GnRH is used as the "targeting agent" and the PE is used for cell killing. Rusiecki et al also teach compositions comprising such.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

a. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 3, 4, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nett et al and further in view of Chaudhary et al (The Journal of Biological Chemistry 265:16306-16310, 1990).

a. The claims recite a targeted fused chimeric toxin comprising (1) the GnRH and (2) a mutated full length PE or domains II and III of PE.

The method in which the targeted fused chimeric toxins were produced is immaterial to their patentability. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product I in the product-by-process claim I is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

b. Nett et al has been described supra. Nett et al does not teach conjugation of the GnRH to domains II and III of PE. This deficiency is made up in the teachings of Chaudhary et al.

c. Chaudhary et al teach mutant forms of PE and PE40.

d. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a targeted fused chimeric toxin comprising (1) GnRH as taught by Nett et al and (2) a mutated form of PE or PE40 which contains domains II and III of PE as taught by Chaudhary et al.

e. One of ordinary skill in the art would have been motivated to produce the claimed invention because Nett et al teach the conjugation of GnRH to toxins including PE. In addition, one of ordinary skill in the art would have been motivated to produce the claimed invention because Chaudhary et al teach "PE40 which does not bind to mouse 3T3 cells and has no detectable cytotoxic activity on mouse 3T3 cells in culture even when tested at 2 μg/ml" (see page 16306). In addition, one of ordinary skill in the art would have been motivated to produce the claimed invention because Chaudhary et al teach studies have shown that domain I has an important role in binding to target cells (see page 16306). Thus, it would have been obvious to conjugate the cell targeting moiety of GnRH for binding to the GnRH receptor and the cell killing moiety of PE40 which lacks the binding domain but retains domains II and III for toxicity.

f. Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention because Nett et al teach that the toxin conjugates resulted in specific killing effects (see page 32). In addition, one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention because Chaudhary et al teach "These data indicate that sequences lying between amino acids 226 and 252 contribute to the cytotoxicity of these molecules" (see page 16306).

g. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

19. Claims 1-7, 9-10, 21, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nett et al, and further in view of Chaudhary et al {a} (Nature 339:394-397, 1989) and Chaudhary et al {b} (Proc. Natl. Acad. Sci. USA 84:4538-4542, 1987).

a. Claims 1-4 and 7 have been described supra. Claims 5-6, 9-10, 21, and 22 recite a method for the production of cancer cell targeted fused chimeric toxins produced by fusing at the DNA level the oligonucleotide encoding ten amino acids of GnRH analog upstream to a mutated form of PE or to a sequence consisting of domains II and III of PE, and a method of producing the chimeric toxin GnRH-PE40 and a plasmid comprising a promoter operably linked to a DNA molecule encoding a targeted fused chimeric toxin, and a method of administering to a patients body by systemic administration the chimeric toxins. For this rejection the term "analog" is being broadly interpreted as (1) a chemically modified form of GnRH or (2) a polypeptide wherein the amino acids at one or more positions have been substituted. For claim 6 applicant is reminded that the intended use of a product claim carries no patentable weight for this rejection [MPEP 2111.02]. With regards to the incomplete method claims 9, 10, and 22 the preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. In re Hirao, 535 F.2d 67, 190 USPQ 15 (CCPA 1976); Kropa v. Robie, 88 USPQ 478, 481 (CCPA 1951).

b. Nett at al has been described supra. Nett et al also teach the ten amino acids of GnRH targeted protein (see Table II and page 12, lines 6-7 where Z can be Gly-NH2). Nett et al also teach modifications to the sequence of GnRH at positions 6 and 10 which result in higher affinity for the GnRH receptor that are 100 times more potent than the parent compound (see page 7, lined 5-7, and page 11, lines 1-4) as well as chemically altering the GnRH molecule. Nett et al also teach production of the toxins by recombinant DNA technology (see pages 11-13) and administering the conjugated toxins to animals intravenously (see page 35, line 33). Nett et al does not teach (1) a plasmid or (2) methods for ligating the oligonucleotide encoding GnRH or a toxin to produce a chimeric toxin molecule or a mutated form of PE or PE encoding for domains I and II. These deficiencies are made up in the teachings of Chaudhary et al {a} and {b}.

c. Chaudhary et al {a} teach a chimeric toxin comprising an immunoglobulin and a mutated form of PE consisting of domains I and II of PE in which PE is the toxic moiety (designated PE-40) and a plasmid which comprises ligating the DNA encoding for the immunoglobulin single chain upstream of the PE wherein said plasmid contains a promoter operably linked to the molecule encoding for such chimeric toxin (see Figure 1 and page 395). Chaudhary et al {a} also teach a method of producing a fusion protein toxin.

d. Chaudhary et al {b} teach a recombinant fusion protein comprising transforming growth factor type alpha and PE 40 wherein PE 40 consists of domains II and III (see Figure 1 and Figure 2). Chaudhary et al {b} also teach a method of producing said fusion protein with

recombinant methods and a plasmid comprising a promoter and an in vitro method of treating cancer cells (see page 4539, Assay of the Biological activity).

e. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a fusion protein comprising the ten amino acids of GnRH, wherein residue(s) have been substituted in GnRH, wherein the oligonucleotide encoding for GnRH is ligated upstream to DNA encoding a mutated form of PE, wherein the fusion protein is produced by recombinant methods, wherein the plasmid encoding for such comprises a promoter, a method for producing such, compositions comprising such, and a method for administering said compositions to a patient.

f. One of ordinary skill in the art would have been motivated to produce the claimed invention because Nett et al teach the amino acid sequence of the GnRH (see page 14, line 20-21). Nett et al also teach a reason to mutate the GnRH at positions 6 and 10 to produce compounds that have higher affinity for the GnRH receptor. In addition, Nett et al teach the use of fusion protein toxins "has great utility in human medicine as well as in veterinary medicine" (see page 14, lines 15-16). One of ordinary skill in the art would have been motivated to produce the claimed invention because Chaudhary et al {a} teach recombinant DNA techniques have been used to produce chimeric toxin fusion proteins in E. coli. And Chaudhary et al fused the "targeting moiety" upstream of the PE toxin (See page 395 and Figure 1). One of ordinary skill in the art would also have been motivated to produce the claimed invention because Chaudhary et al {b} teach "A PE molecule which domain I has been deleted (PE40) has full ADP-

ribosylation activity but has extremely low cell-killing activity because of loss of the cell-recognition domain" (see page 4538) and "We have now began to use PE40 to construct chimeric proteins in which growth factor genes or other genes have been replaced domain I to impart new and specific cell recognition properties" (see page 4538). In addition, One of ordinary skill in the art would have been motivated to produce the claimed invention by recombinant DNA techniques because Chaudhary et al {b} teach chemical conjugation of proteins to toxins result in nonspecific toxicity due to incomplete inactivation of domain I and this nonspecific toxicity is much diminished in genetically engineered chimeric PE40 toxin fusion proteins. (See page 4542). Moreover, one of ordinary skill in the art would have been motivated to produce the claimed invention because Chaudhary et al {b} teach the fusion toxin protein targeted cancer cells and resulted in cell killing activity.

g. Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention because Chaudhary et al {b} teach the fusion protein toxin molecule comprising a deleted form of PE "has high cell-killing activity against cells "expressing the receptor and not against cells producing insufficient levels of receptor (see page 4541, discussion). Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention because Chaudhary et al {a} teach they have constructed a recombinant fusion protein toxin by DNA methods in E. coli using the modified form of Pseudomonas exotoxin. (See page 396, last paragraph).

h. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

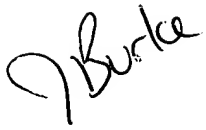
Conclusions

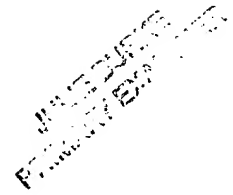
20. No Claims are allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

22. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,





Larry R. Helms Ph.D.

703-306-5879